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Development of New Coronary Atherosclerotic Lesions During a 4-Year Multifactor Risk Reduction Program: The Stanford Coronary Risk Intervention Project (SCRIP)

THOMAS G. QUINN, MD, EDWIN L. ALDERMAN, MD, FACC, ALEX McMILLAN, PhD, WILLIAM HASKELL, PhD, FACC, FOR THE SCRIP INVESTIGATORS

Stanford, California

Objectives. **This study attempted to determine whether an intensive multifactor risk reduction program conducted over 4 years would reduce the rate of development of new coronary artery lesions.**

Background. **Recent angiographic trials have generally demonstrated that normalization of plasma lipoprotein profiles reduces the rate of progression of established coronary lesions, but limited data exist on how these treatments influence the development of new lesions.**

Methods. **Three hundred men and women with coronary artery disease were randomized to multifactor risk reduction or usual care. Highly significant improvements in risk factors were achieved by the risk reduction group compared with minimal changes by the usual care group. Quantitative coronary angiography was performed on entry and after 4 years under identical conditions. A decrement in the minimal diameter of visually normal segments >0.2 mm was considered to indicate new lesion formation.**

Results. **A total of 1,605 segments, representing 257 patients, were considered normal at baseline, with 804 and 801 disease-free segments in the usual care and risk reduction groups, respectively. Ninety-nine segments (6.1%) were identified by follow-up quantitative angiography and two angiographic observers as having new lesion formation (usual care 7.6%, risk reduction 4.7%, $p = 0.05$). New lesion formation was observed in 41 (31%) of 131 patients in the usual care group and in 29 (23%) of 126 patients in the risk reduction group ($p = 0.16$), with a mean number of new lesions/patient of 0.47 in the usual care group and 0.30 in the risk reduction group ($p = 0.06$). Multiple regression analysis identified on-study dietary fat intake as the best correlate with new lesion formation.**

Conclusions. **These data indicate that intensive multifactor risk reduction tends to diminish the frequency of new coronary lesion formation.**

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The lipid infiltration theory promoted by Duff and McMillan (1) in the early 1950s was the basis for numerous large epidemiologic investigations that have linked elevations in serum cholesterol to coronary atherosclerotic disease (2–8). Subsequently, numerous trials utilizing clinical end points to assess the efficacy of lipid management in patients at risk for (or with overt) coronary artery disease have been performed (4,9–13). Typically, a reduction in cardiovascular events was observed and correlated with a favorable change in the lipid profile. Both pharmacologic and nonpharmacologic intervention trials using angiographic end points have since evolved (14–23). These studies consistently revealed a positive association between the degree of improvement in the lipid profile and angiographic evidence of a decrease in the progression of established coronary artery disease. Some studies also revealed a significant degree of disease regression as well (14,16,18,21,22,23).

If lipid infiltration is inciting vascular injury that leads to the development of coronary artery disease, intensive management of dyslipidemias might be associated with less new lesion development. However, relatively few clinical trials designed to influence the lipid profile have specifically addressed the rate of new lesion development as a function of favorable risk factor modification for coronary atherosclerosis. To our knowledge, only the Cholesterol Lowering Atherosclerosis Study (CLAS) (24) has reported an effect of a lipoprotein intervention on the rate of new coronary atherosclerotic lesion development. Also, several studies (25,26) have provided preliminary evidence that calcium channel blockers, which do not change the lipid profile, may reduce the rate of new lesion formation.

We hypothesized that the incidence of *new* atherosclerotic lesions in the coronary vasculature would be reduced signifi-

From the Division of Cardiovascular Medicine and the Center for Research in Disease Prevention, Stanford University School of Medicine, Stanford California. Financial support was provided by Research Grant HL-28292 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and a gift from the Claude R. Lambe Charitable Foundation, Wichita, Kansas. Dr. Quinn was supported in part by Preventive Cardiology Postdoctoral Training Grant 5T32 HL-07034 from the National Heart, Lung, and Blood Institute. The complete list of SCRIP Investigators appears in Ref 23.

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Address for correspondence: Dr. Edwin L. Alderman, Division of Cardiovascular Medicine, Cardiovascular Research Building, Stanford University School of Medicine, Stanford, California 94305.

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cantly after an intervening period of intensive multiple risk factor reduction in subjects with angiographically documented coronary artery disease. The hypothesis was tested by a review of angiographic data from the Stanford Coronary Risk Intervention Project (SCRIP).

Methods

Study patients. The SCRIP study and design have been described elsewhere (23). In brief, SCRIP was a randomized, multiple risk factor intervention trial using angiographic end points. It was conducted over 4 years in men and women with coronary artery disease with the goal of altering the rate of coronary artery lumen narrowing. The participants were randomized to the usual care of their own physician or to an individualized, multifactor, risk reduction program. Three hundred patients (259 men, 41 women; mean [±SD] age 56 ± 7.4 years) with angiographically defined coronary atherosclerosis were randomly assigned to usual care (n = 155) or multifactor risk reduction (n = 145). Computer-assisted quantitative coronary arteriography was performed at baseline and at 4 years. The study protocol and progress were reviewed before the start and annually by the Stanford University Panel on Human Subjects in Medical Research, by committees on the use of human subjects at each of the participating hospitals and by an external Safety and Data Monitoring Committee appointed by the National Heart, Lung, and Blood Institute. Informed consent was obtained from all subjects before study enrollment.

SCRIP risk reduction program. Patients assigned to risk reduction were provided individualized programs involving a low fat, low cholesterol diet; exercise; weight loss; smoking cessation, and medications to favorably alter lipoprotein profiles. All risk reduction group subjects were instructed by a dietitian in a low-fat, low-cholesterol and high-carbohydrate diet with a goal of <20% of energy intake from fat, <6% from saturated fat and <75 mg of cholesterol/day. A physical activity program was recommended consisting of an increase in daily activities, such as walking, climbing stairs and household chores and a specific endurance exercise training program. A staff psychologist developed an individualized stop-smoking program for smokers in the risk reduction group. A major goal was to decrease low density lipoprotein (LDL) cholesterol to <110 mg/dl (2.84 mmol/liter), to decrease triglyceride concentrations <100 mg/dl (1.13 mmol/liter) and to increase high-density lipoprotein (HDL) cholesterol concentrations >55 mg/dl (1.42 mmol/liter). If the SCRIP staff concluded it unlikely that a subject in the risk reduction group would meet the maximal LDL cholesterol goals within the first year without drug therapy, a cholesterol-lowering drug regimen was added.

Risk factor evaluations. All subjects had their clinical status and risk factors evaluated at baseline before randomization and annually for 4 years. Blood pressure was measured three times after a 5-min rest and with the subject seated using a Hawksley random-zero sphygmomanometer. Skinfolds were measured in triplicate at the subscapula, triceps and suprailiac crest and summed to represent general adiposity. Reported smoking status was verified by measuring the carbon monoxide content of expired air using an Ecolyzer (27) and the thiocyanate concentration in plasma (28). Symptom-limited treadmill exercise testing was performed using a Balke-type protocol. Dietary intake was determined by 4-day food records using the Nutrition Coordinating Center protocols for data collection and coding and version 13 data base for data analysis (29). Physical activity was reported using the Stanford 7-day physical activity recall (30) and other questions that solicited information on the frequency of participating in specific leisure-time and conditioning activities.

At baseline and annually, fasting concentrations plasma lipids and lipoproteins were measured during two clinic visits. The two values were averaged for each subject to represent the subject at baseline and for each year in the study. Plasma concentrations of total cholesterol and triglycerides were measured in the Stanford Lipoprotein Research Laboratory by enzymatic procedures (ABA 200 instrument, Abbott Laboratories) (31,32). The HDL cholesterol was measured by dextran sulfate–magnesium precipitation (33), followed by enzymatic determination of cholesterol. The laboratory remained certified by the Centers for Disease Control and Prevention lipid standardization program (34). Lipoprotein(a) concentration was measured by an enzyme-linked immunoasay (ELISA) kit [Macra lipoprotein(a), Terumo Dianostics Division] described previously (35,36). The LDL plus intermediate density lipoprotein apolipoprotein B concentration was measured by standardized ELISA use of of two monoclonal capture antibodies (Medix Biotech) (37). Plasma glucose concentration was measured using the glucose oxidase method (38) and insulin concentration by radioimmunoassay (39).

SCRIP angiographic acquisition protocol. Baseline coronary arteriograms were obtained in a uniform manner at baseline and follow-up with the requirement that nitroglycerin be administered before coronary injections. Coronary catheters with metallic cylindric markers near their distal end provided a sharp calibration edge for quantitation, which reduces measurement variation when computer-assisted measurement techniques are used (40). SCRIP required that neither the qualifying segment nor any vessel proximal to it contained a lesion ≥70% in diameter reduction and that the vessel had neither been grafted nor instrumented by a previous revascularization procedure. Subjects were eligible for the study if at least one major coronary artery showed a segment with lumen narrowing between 5% and 69% that was unaffected by revascularization procedures. Visually normal segments (<5% narrowing in lumen diameter) were quantitated at enrollment; however, these segments were not included in the primary analysis of the SCRIP hypothesis.

All consenting subjects had protocol-mandated follow-up arteriograms obtained 4 years after the baseline arteriogram. Use of marker catheters, before nitroglycerin administration and replication of projection angles were performed as at the baseline study. If a subsequent 4-year arteriogram was not obtainable, the results of earlier clinically indicated angio-

grams were included as long as the interval between the baseline and follow-up angiogram was >12 months and the clinically indicated angiogram was performed according to the research protocol.

The quantitative coronary angiographic system used in this study was developed at Stanford Medical Center to measure coronary vessels on 35-mm cineangiograms. Its design, accuracy, precision and intraobserver and interobserver variability have been previously reported (41). The system has two cine film digitizers that simultaneously process paired coronary arteriograms for evaluation of serial changes in coronary arteries. A pair of video monitors for each projector allow the operator real-time viewing of the film for frame selection. Comparable segments on baseline and follow-up angiograms were digitized. The operator manually defined approximate edges, and an automatic edge-finding algorithm defined matching segment lengths and the margins for measurement of mean and minimal diameters. The operator had no knowledge of patient randomization assignment.

Angiographic assessment of new lesion formation in the SCRIP data base. Two experienced angiographic observers (with no knowledge of patient randomization assignment) visually assessed each segment that had an interval reduction in minimal diameter >0.2 mm within a segment previously considered normal. In the SCRIP analysis, individual diseased segments were categorized as progressing, regressing or unchanged on the basis of whether the minimal diameter of diseased segments changed by >0.2 mm. This threshold of 0.2 mm was based on a threefold multiple of the within-procedure measurement variability (SD 0.033 mm) and further multiplying by a factor of 2 to account for between-procedure variation (40).

By simultaneous side-by-side comparison, the baseline and follow-up angiograms were compared visually. The identical projections of the baseline and follow-up angiograms were simultaneously displayed on the two monitors. From these matched views, the precise frame on which quantitative coronary edge detection analysis suggested new lesion development for the segment of interest was displayed. Visual assessment for interval coronary segment change was based on both static images and dynamic display at variable rates to confirm or refute serial change. Results of the visual assessment were recorded as three possible outcomes: no apparent change, definite new lesion or previous disease present with progression.

Statistical analysis. For within-group comparisons from baseline to on-study, one-sample *t* tests were used. The significance of differences in risk factors or angiographic measures between the usual care and risk reduction groups or between the "no new lesion" and "new lesion" groups were determined by two-sample *t* tests, chi-square or a Wilcoxon test for two samples. Per-segment analysis adjusting for within-patient correlations for the development of new lesions were performed by fitting a beta-binominal model (42). Univariate and multivariate logistic regression analyses were performed to determine which body composition, dietary, clinical or laboratory variables were associated with new lesion formation. Body composition variables analyzed included weight, relative weight, body mass index, skinfolds and waist/hip ratio. Dietary variables were total fiber intake (g); soluble fiber intake (g); percent of total calories from total fat, saturated fat, monounsaturated fat, polyunsaturated fat and alcohol; polyunsaturated/saturated fat ratio intake; cholesterol intake (mg/day); and calories consumed/kg body weight. Laboratory variables included plasma triglycerides, cholesterol, LDL cholesterol, HDL cholesterol, total cholesterol/HDL ratio, apolipoprotein B, apolipoprotein(a) and fasting/postprandial glucose and insulin concentrations. Clinical variables analyzed included systolic and diastolic blood pressure, maximal metabolic equivalents (METs) achieved on treadmill testing and the Framingham coronary heart disease risk score (43). Significance was set at $p < 0.05$.

Results

Results of the SCRIP study have been previously reported (23). The intensive risk reduction resulted in significant improvements in various risk factors, including LDL cholesterol (−23%), HDL cholesterol (+12%), plasma triglycerides (−20%), body weight (−4%), exercise capacity (+20%) and the intake of dietary fat (−24%) and cholesterol (−40%) compared with relatively small changes in the usual care group. The risk reduction group showed a rate of narrowing of diseased coronary artery segments that was 47% less than that of subjects in the usual care group ($p < 0.02$) over the 4 years of the study. There was a significant reduction in the number of cardiac events requiring hospital admission in the risk reduction group relative to the usual care group (25 and 44, respectively, $p = 0.05$).

Of the 300 subjects randomized in SCRIP, 274 (91%) completed follow-up arteriograms, and 257 (86%) had comparative measurements of segments that were free of disease at baseline and adequately visualized in follow-up. Of the 17 arteriograms excluded from analysis for technical reasons, 11 were due to the patients' failure to follow the nitroglycerin protocol at baseline or follow-up, 3 to inadequate film quality, 2 to revascularization procedures that eliminated all eligible segments, and 1 to normal SCRIP-eligible segments. The risk intervention and risk factor status at baseline and on-study for the 257 patients included in this report are presented in Table 1. These 257 subjects had 1,647 coronary artery segments identified as visually normal (<5% stenosis) at baseline. Of these, quantitative coronary angiography identified 491 segments that had a >0.2 mm reduction in minimal lumen diameter between entry and follow-up angiogram. Subsequent visual assessment of these segments revealed that, in retrospect, 42 of these segments had previous disease at baseline. In the remaining 1,605 visually normal segments, 99 new lesions were identified (Fig. 1). The frequency of new lesion formation was compared for subjects randomized to usual care versus risk reduction on a patient-by-patient and segment-by-segment basis.

Table 1. Baseline Versus On-Study Risk Intervention Values and Risk Factor Measurements for the Usual Care and Risk Reduction Groups (mean values)

	Baseline UC + RR (n = 257)	On Study		RR Change From Baseline (%)
		UC (n = 131)	RR (n = 126)	
Dietary saturated fat (% cal)	10.0	10.6	6.8	−2.9*
Dietary cholesterol (mg/day)	260	273	142	−94*
Performance of daily activities	1.78	1.95	2.20	0.46†
Current cigarette user (%)	13.7	16.8	10.4	−0.0
Hypolipidemic drugs (% patients)	9.0	30.7	93.3	80.7*
Body composition				
Weight (kg)	82.0	85.8	77.8	−3.6*
Body mass index (kg/m^2)	27.0	27.5	26.0	−3.3*
Blood pressure				
Systolic (mm Hg)	119.2	121.1	120.4	−0.2
Diastolic (mm Hg)	71.3	72.3	69.6	−1.6
Exercise test, max MET level	8.9	9.8	10.4	+19.0*
Lipid profile				
Total cholesterol (mg/dl)	229.5	222.9	195.1	−16.4*
LDL cholesterol (mg/dl)	156.6	149.6	121.0	−23.5*
HDL cholesterol (mg/dl)	44.0	44.8	50.9	+11.9*
Triglycerides (mg/dl)	153.5	156.4	128.9	−17.3*
Glucose tolerance				
Fasting glucose (mg/dl)	104.4	111.1	101.0	−2.8
1-h postload glucose (mg/dl)	156.7	164.2	137.0	10.7*
Framingham risk score	14.6	14.1	10.8	−26.9*

*$p < 0.01$. †$p < 0.05$. HDL = high density lipoprotein; LDL = low density lipoprotein; RR = risk reduction; UC = usual care; max MET = maximal metabolic equivalent.

Per-patient analysis. The minimal diameters of normal segments at baseline that did not develop new lesions were 2.30 and 2.32 mm for the usual care and risk reduction groups, respectively ($p = 0.70$) (Table 2). The baseline minimal diameter of normal segments for patients in the risk reduction group who developed new lesions was significantly smaller than for those in the usual care group (2.55 vs. 3.05 mm, $p = 0.01$, for risk reduction and usual care, respectively). The percent of all subjects (n = 257 [usual care, n = 131; risk reduction, n = 126]) with at least one new lesion was lower for the risk reduction group. However, this difference was not statistically significant (usual care [n = 41], 31.3%; risk reduction [n = 29], 23.0%, $p = 0.16$). The majority of these 70 patients with new lesions had no more than one new lesion identified. The remaining subjects had predominantly two new lesions identified, and a small percent had three or four new lesions. The average number of new lesions/patient was 0.47 for the usual care group and 0.30 for the risk reduction group ($p = 0.06$).

Per-segment analysis. By a per-segment analysis (Table 3) adjusted for within-subject correlation of new lesion formation, baseline minimal diameters for diseased and nondiseased segments were not significantly different between the usual care and risk reduction groups. The percent of all normal segments at enrollment with new lesion formation was significantly lower for those subjects participating in the risk reduction program than for patients assigned to usual care (usual care [n = 61], 7.6%; risk reduction [n = 38], 4.7%, $p = 0.02$). When the within-patient correlation for new lesion formation is taken into account using a beta-binomial model, the level of significance increases to 0.05.

New lesion size. With respect to only new lesions, the absolute change in minimal diameter was compared for the risk reduction group versus usual care group by a segment-by-segment and a per-patient analysis. Sixty-one new lesions were identified in the usual care group, and the mean and median reductions in minimal diameter were 0.62 and 0.57 mm, respectively (range 0.2 to 1.54) (Table 3). There were 38 new lesions identified among the risk reduction group, and the mean and median reductions in minimal diameter were 0.69 and 0.56 mm, respectively (range 0.22 to 4.69). There were no significant differences in the degree of mean or median diameter reduction for the two groups on a per-segment or per-patient analysis.

New lesions and clinical correlates. Clinical correlates of new lesion formation were assessed using univariate and multivariate analysis (Table 4). For the univariate analysis 29 potentially influential variables were evaluated for association with new lesion development. These variables reflect body composition, dietary intake, laboratory values and clinical variables (see Methods). The extent to which these variables discriminated between the development of new lesions versus no new lesions was evaluated. These variables were measured at baseline and on-study. The on-study values were an average of year 1, 2, 3 and 4 annual assessments. First, the usual care and risk reduction groups were combined and analyzed for

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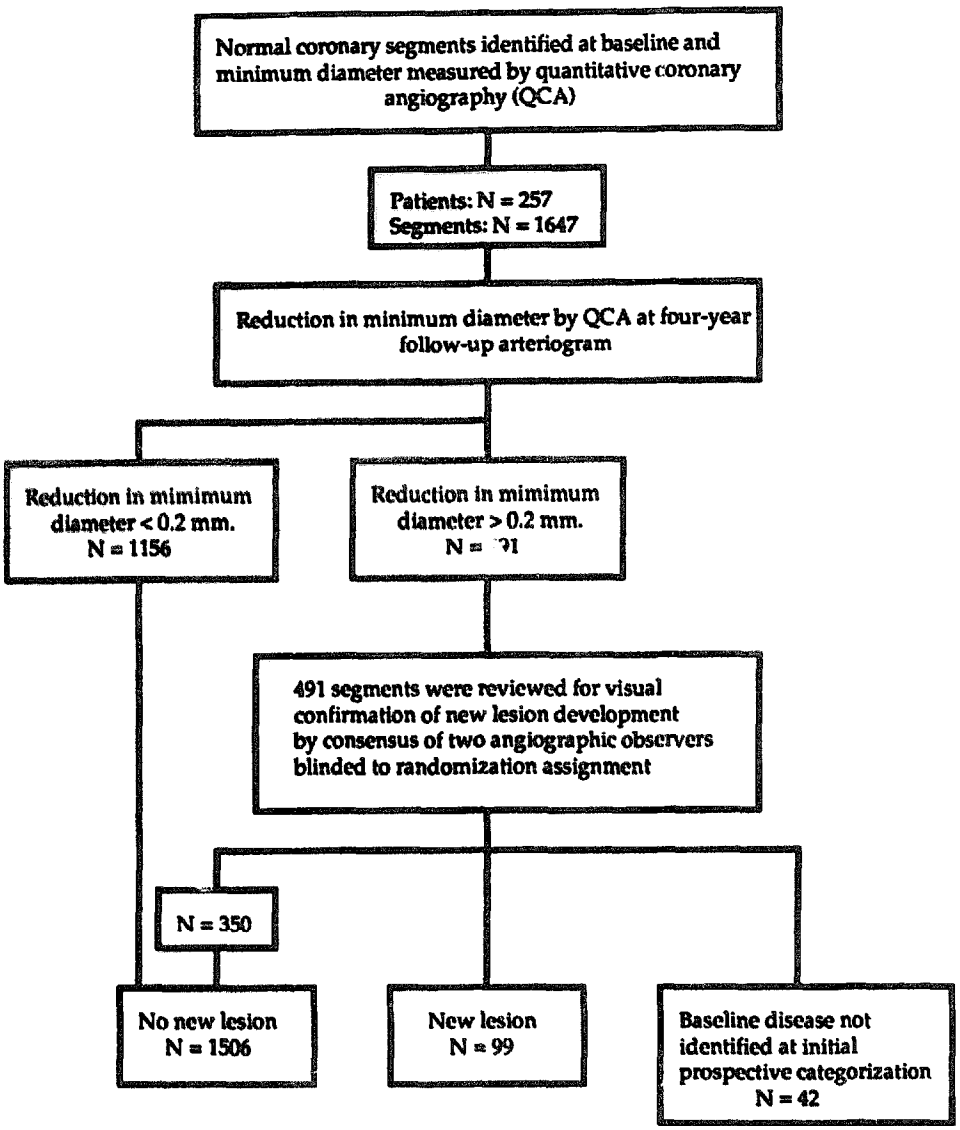

Figure 1. Categorization of individual segments, showing a new lesion or not, based on a combination of computer-assisted quantitation at entry and 4-year concluding angiograms combined with visual confirmation of new lesion development.

clinical correlates (on a per-patient basis) for the formation of at least one new lesion versus no new lesions. Diastolic blood pressure was significantly lower at entry among patients who did not develop new lesions (no new lesions 70.6 mm Hg; new lesions 73.1 mm Hg, $p = 0.04$). Otherwise, there were no significant differences at baseline. Analysis of on-study clinical variables revealed significantly lower values in the no new lesion category for percent dietary, saturated, monounsaturated and polyunsaturated fat and dietary cholesterol. The percent of dietary carbohydrate intake was significantly higher in the no new lesion category. A reduction in dietary percent fat from baseline to on-study was associated with the absence of new lesions. A reduction in serum LDL and total cholesterol was correlated with no new lesion formation. Reductions from baseline to on-study in total cholesterol, LDL cholesterol, total cholesterol/HDL cholesterol ratio, fasting glucose and the Framingham risk score were also associated with an absence of new lesion development.

A logistic regression analysis was performed using the following variables: on-study smoking rate, dietary cholesterol and percent fat; change in LDL/HDL ratio, serum LDL and HDL concentrations, diastolic blood pressure and Framingham risk score. In this analysis no variable had greater significance than the dietary percent of calories from fat. The coefficients from this analysis indicate that patients obtaining 40% of their calories from fat had a 39% chance of developing at least one new lesion in the course of 4 years, whereas patients who obtained 20% of their calories from fat had a 19% chance of a new lesion developing.

The correlation between progression or regression of established coronary artery disease at baseline and the incidence of new lesion formation was evaluated. In the SCRIP trial, it was reported that there were 10.3% of patients in the usual care group versus 20.2% of patients in the risk reduction group in the regression category and nearly equal numbers of patients from both groups in the progression category (usual care

Table 2. Per-Patient Analysis of New Lesion Formation in the Usual Care and Risk Reduction Groups

	UC	RR	p Value
Pts with qualifying angiograms	131	126	
Pts with new lesions	41 (31.3%)	29 (23.0%)	0.16
Min segment diameter, baseline (mm)	3.05 ± 0.80	2.55 ± 0.74	0.01
Min segment diameter, follow-up (mm)	2.43 ± 0.80	2.01 ± 0.59	0.01
4-year change (mm)	−0.62 ± 0.23	−0.54 ± 0.37	0.30
Median 4-year change (mm)	−0.60	−0.46	0.30
Range in 4-year change (mm)	−0.22 to −1.18	−0.22 to −2.11	
Pts without new lesions	90	97	
Min segment diameter, baseline (mm)	2.30 ± 0.44	2.32 ± 0.50	0.70
Min segment diameter, follow-up (mm)	2.26 ± 0.44	2.29 ± 0.51	0.72
4-year change (mm)	−0.03 ± 0.17	−0.03 ± 0.18	0.97
Pts with 1 new lesion	23	22	
Pts with 2 new lesions	17	5	0.08
Pts with ≥3 new lesions	1	2	
Average no. of new lesions/pt	0.47	0.30	0.06

Data presented are mean value ±SD or number of patients (Pts). Min = minimal; pt = patient; other abbreviations as in Table 1.

Table 4. Clinical Correlates of New Lesion Formation by Univariate Analysis of Variables Significantly Correlated With New Lesion Development

	No New Lesion	≥1 New Lesion	p Value
Baseline diastolic BP (mm Hg)	70.6 ± 8.9	73.1 ± 8.4	0.04
On-study (% of calories)			
Fat	27.3 ± 7.9	30.8 ± 9.6	0.008
Saturated fat	8.4 ± 3.3	9.7 ± 4.4	0.030
Monounsaturated fat	10.2 ± 3.5	11.6 ± 4.0	0.012
Polyunsaturated fat	6.5 ± 1.7	7.2 ± 1.7	0.006
Carbohydrate	51.5 ± 9.6	47.6 ± 10.4	0.007
On-study dietary chol (mg/dl)	196 ± 116.4	243 ± 147.0	0.017
Change from entry to on-study			
% of dietary fat	−4.3 ± 8.1	−2.1 ± 7.8	0.050
Plasma chol (mg/dl)	−23.4 ± 35.8	−11.5 ± 32.4	0.012
LDL chol (mg/dl)	−24.2 ± 33.6	−12.4 ± 28.1	0.005
Total chol/HDL chol	−0.89 ± 1.26	−0.53 ± 0.3	0.020
Glucose, fasting	−0.20 ± 28.1	7.7 ± 22.1	0.063
Framingham risk score	−2.5 ± 4.5	−1.3 ± 3.5	0.030

Only variables with $p \leq 0.05$ are listed. BP = blood pressure; chol = cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein.

49.6%; risk reduction 50.4%) (23). Patients with no change represented 19.7% of the usual care group and 17.6% of the risk reduction group. Patients with mixed changes represented 20.5% of the usual care group and 11.8% of the risk reduction group. In this analysis, the presence of new lesions versus no new lesions was compared among only those patients with progressing disease and those with regressing disease in the main SCRIP study. There were 160 patients in the disease progression-only and disease regression-only categories. Of these patients, 45 developed new lesions, and 115 did not. Among the patients who did not develop new lesions, 30 (26%) were pure regressors, and 85 (69%) were pure progressors. For the new lesion group, 7 (16%) were pure regressors, and 38 (84%) were pure progressors. The difference in the incidence of no new lesions and new lesions among patients with only disease progression or regression was not statistically significant.

Table 3. Per-Segment Analysis of New Lesion Formation in the Usual Care and Risk Reduction Groups

	UC	RR	p Value
No. of visually normal segments	804	801	
Segments without new lesions	743	763	
Min segment diameter, baseline (mm)	2.29 ± 0.77	2.28 ± 0.81	0.82
Min segment diameter, follow-up (mm)	2.25 ± 0.76	2.24 ± 0.80	0.85
4-year change (mm)	−0.04 ± 0.28	−0.04 ± 0.25	0.93
Segments with new lesions	61 (7.6%)	38 (4.7%)	0.02
Min segment diameter, baseline (mm)	3.03 ± 0.77	2.70 ± 0.91	0.07
Min segment diameter, follow-up (mm)	2.40 ± 0.75	2.06 ± 0.79	0.03
4-year change (mm)	−0.62 ± 0.29	−0.64 ± 0.72	0.88
Median 4-year change (mm)	−0.57	−0.52	0.19
Range in 4-year change (mm)	−0.21 to −1.54	−0.22 to −4.69	

Data presented are mean value ±SD or number of segments. Abbreviations as in Tables 1 and 2.

In SCRIP, differences in rates of change of minimal diameter between the usual care and risk reduction groups were somewhat greater for women than men. However, in this evaluation there were no significant gender differences in the rate of new lesion formation (226 men with 63 new lesions [28%]; 31 women with 7 new lesions [23%], p = 0.67).

New lesion formation and pharmacologic therapy. The potential for a pharmacologic influence on the formation of new lesions was assessed. Calcium channel antagonists and hypolipidemic agents (bile acid sequestrants, lovastatin, gemfibrozil, niacin) were chosen for evaluation. Our analysis was based on the administration of one or more of these drugs during the fourth year of the study. Ninety-eight subjects received calcium channel antagonists, 47 of whom were in the usual care group and 51 in the risk reduction group. Twenty-six percent of the drugs were of the dihydropyridine class. Of these 98 subjects, 27 (28%) developed new lesions compared with 27% of subjects not taking calcium blocking drugs (p = NS).

One hundred forty-three patients were taking hypolipidemic drugs, 35 of whom were in the usual care group and 108 in the risk reduction group. Thirty-eight percent of the patients were taking niacin; 67% were taking bile acid–binding resin; and 41% were taking an HMG-CoA reductase inhibitor. Of these 143 subjects, 29 (20%) developed new lesions compared with 41 (36%) not taking hypolipidemic drugs ($p < 0.01$).

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Discussion

Rate of new lesion formation. In this study, coronary artery segments that were visually normal on entry developed angiographic evidence of new atherosclerotic lesions at a significantly lower rate in patients in the risk factor reduction group than in those in the usual care group (rate of new lesion formation: usual care 7.6%; risk reduction 4.7%, p = 0.05). On a per-patient basis there was a trend favoring fewer new lesions among those in the risk reduction group; however, it was not statistically significant (for patients with new lesions, usual care 31%, risk reduction 23%, p = 0.16). This could be explained by the substantial difference in statistical power for the two types of analyses (for per-segment analysis, n = 1,605; for per-patient analysis, n = 257).

For the purpose of this study, new lesion formation was defined as a decrease in minimal diameter of a predefined coronary artery segment >0.2 mm and confirmed on visual assessment as representing a lesion. The inherent limitations of angiography, however, preclude strictly labeling these segments as normal at baseline. Theoretically and very likely, concentric atherosclerotic disease or minimal focal disease, which tends to be concentric and thus not readily detectable as a lumen irregularity on arteriography, may not have been recognized at enrollment. Thus, this analysis may have as much to do with disease progression of small lesions as it does with the formation of new lesions. The use of intravascular ultrasound in future studies of new lesion formation should help to alleviate this problem. However, there is no obvious reason why the usual care or risk reduction groups would be disproportionately affected by these limitations in angiographic detection of atherosclerotic disease. Therefore, we conclude that the somewhat lower rate of new lesion formation for the coronary segments exposed to intensive risk factor intervention does signify a decrease in atherogenesis.

New lesions and clinical correlates. Combining the risk reduction and usual care groups, and comparing baseline characteristics for those who developed new lesions versus those who did not, revealed similar profiles. Among the 29 variables assessed, only diastolic blood pressure differed significantly between the two groups. It is unlikely that this relatively small baseline difference in diastolic blood pressure (2.5 mm Hg, p = 0.04) significantly influenced the rate of new lesion formation. The on-study differences in diastolic blood pressure were also different between those subjects with and without new lesions (2.3 mm Hg, p = 0.04). This relation between diastolic blood pressure and new lesion formation in SCRIP is similar to the relation of blood pressure change produced by nicardipine and new lesion formation reported by Waters et al. (25).

The a priori hypothesis states that multiple risk factor intervention would result in a diminished rate of new lesion formation. All variables that differed significantly for no new lesion and new lesion groups were consistent with the study hypothesis. This study showed a strong correlation between on-study dietary fat (percent total, saturated, monounsaturated and polyunsaturated fat), cholesterol intake and the incidence of new lesion formation. Furthermore, reductions in dietary cholesterol and total fat intake, serum LDL and total cholesterol concentration, total cholesterol/HDL cholesterol ratio and fasting glucose concentrations correlated with the absence of new lesion formation. A stepwise logistic regression analysis assigns the difference in new lesion formation predominantly to the percent of calories consumed as fat. This relation of dietary fat intake to new lesion formation is consistent with the results from the only other published data on new lesion formation in an angiographically based trial (Cholesterol Lowering Atherosclerosis Study [CLAS]) (24). In that study each quartile of increased consumption of total and polyunsaturated fat was associated with a significant increase in the risk of developing new lesions. Placebo recipients in the CLAS in whom new lesions did not develop increased dietary protein to compensate for reduced intake of fat by substituting low fat meats and dairy products for high fat meats and dairy products. Similarly, SCRIP participants randomized to the risk reduction group preferentially increased carbohydrate intake to offset caloric deficits induced by dietary fat restriction.

Confounding issues pertinent to the association of no new lesion formation and dietary fat intake were assessed. Body composition, Framingham risk score, blood pressure and maximal METs were not significantly different between the patients with new lesions and those with no new lesions. Multiple regression analysis confirms the potent effect that dietary fat intake had on new lesion formation. Speculation exists with regard to potential mechanisms of coronary atherogensis induced by dietary fat intake that are not reflected in the standard lipid profile. Dietary fatty acids have been shown to influence a variety of arterial wall processes, such as endothelial permeability, thrombosis and inflammatory responses (44,45). Results of this study and those from CLAS demonstrate that a reduction in dietary fat intake decreases the rate of new lesion formation by mechanisms not limited to LDL reduction.

New lesion formation and pharmacologic therapy. Antiatherosclerotic effects of calcium channel blockers have been hypothesized, and incidence of new lesions has been reported in animals and randomized, placebo-controlled intervention trials using these agents (25,26). Although the overall progression of coronary artery disease was not influenced, nifedipine and nicardipine have been shown to decrease the rate of new lesion development or the progression of minimally diseased segments (25,26,46–50). In this study, we assessed the frequency of new lesion formation as a function of calcium channel antagonist or hypolipidemic drug administration during the fourth year. For calcium channel antagonists there was no significant difference or trend that suggested an influence on new lesion formation. Possible explanations for this lack of association include a differential effect among calcium channel antagonists, insufficient sample size, insufficient duration of drug administration and no cause-and-effect relation.

Administration of one or more hypolipidemic agents during the fourth year was associated with a significant reduction in

the rate of new lesion formation. The obvious explanation is that these agents mediate a reduction in new lesion formation by favorably influencing the lipid profile. This is consistent with the univariate analysis that revealed a correlation between new lesions and reductions in serum LDL and the total cholesterol/HDL cholesterol ratio. Other potential mechanisms for an influence on new lesion formation by these hypolipidemic agents cannot be determined from these results.

Study implications. We found that angiographically normal coronary artery segments subjected to improvement in risk factors tended to develop fewer visually evident new atherosclerotic lesions. This reduction correlated best with dietary fat intake and leads to speculation that dietary fat may influence atherogenesis independent of changes in LDL concentration. Other potential correlations may have been lost because of a lack of statistical power in performing a patient-by-patient analysis. In SCRIP and other angiographic trials, a significant reduction in the progression of coronary atherosclerotic disease has resulted from successful risk factor modification. However, in absolute terms, the decrement in lumen encroachment has been small. This raises the question of plaque stability and atherogenesis as it may pertain to a reduction in clinical events, as observed in SCRIP and other trials (9,14,15,21). These are important clinical questions and warrant further investigation, although definitive answers will be difficult to obtain given the many limitations in serially imaging coronary arteries in humans.

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